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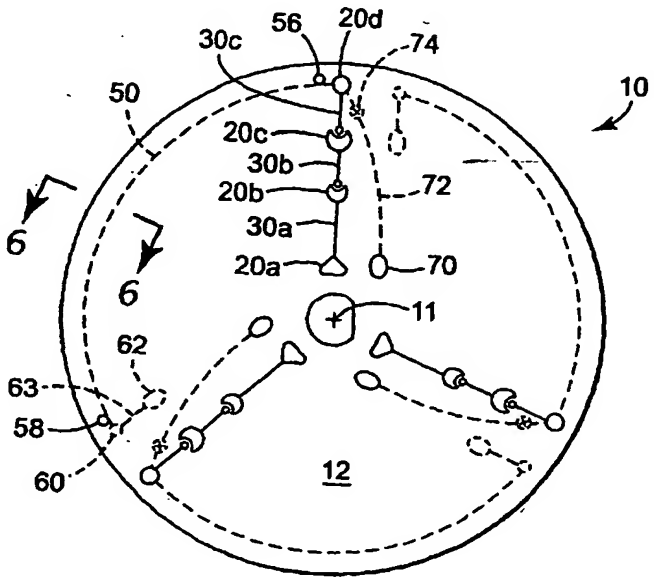
(54) Title: SAMPLE PROCESSING DEVICE WITH INTEGRAL ELECTROPHORESIS CHANNELS



(57) Abstract: Sample processing devices (10) with electrophoresis channels (50) and methods of loading the electrophoresis channels (50) with electrophoresis sieving polymer while rotating the sample processing device (10) are disclosed. In some instances, the electrophoresis channels (50) may be arranged radially relative to the axis of rotation (11) of the sample processing device (10). In other sample processing devices, the electrophoresis channels may be arranged in curved arcs that are concentric about the center of the sample processing device (which preferably corresponds to the axis of rotation).

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SAMPLE PROCESSING DEVICE WITH INTEGRAL ELECTROPHORESIS CHANNELS

GRANT INFORMATION

The present invention may have been made with support from the U.S. Government under NIST Grant No. 70NANB8H4002. The U.S. Government may have certain rights to the inventions recited herein.

FIELD OF THE INVENTION

The present invention relates to the field of sample processing devices and methods. More particularly, the present invention relates to sample processing devices with integral electrophoresis channels and methods of loading the electrophoresis channels with an electrophoresis sieving polymer.

BACKGROUND

The preparation of a biological sample for, e.g., DNA sequencing and detection can involve a number of critical processes and transfers. For example, a user may be required to prepare a biological sample input (e.g., purified DNA target, whole blood/tissue, etc.) and extraction/clean-up. After these steps are completed, the sample materials may typically undergo polymerase chain reaction (PCR) amplification, clean-up and possible detection. The prepared PCR amplification products may then undergo Sanger amplification and clean-up. Following these steps, the end product of the processed sample material may undergo electrophoresis and fluorescence detection.

Each of these procedures can require considerable human intervention and a number of fluid transfers, all of which can result in errors, contamination, and exposure to potential biohazards. Furthermore, the time required from sample input to sequence data output can, in some instances be up to 24 hours or more. In addition, the various equipment required to perform the different procedures may cost, e.g., US$100,000 to about US$200,000 or more, thereby increasing the cost of the processing. Further, the personnel performing these procedures are typically highly-skilled, with expertise in DNA sample preparation, machine interface/maintenance, analysis and quality control.

followed by the electrophoresis sieving polymer during loading of the electrophoresis channel. The flow restrictor may be, e.g., a closed valve that prevents fluid flow until opened, or it may be in the form of a constricted passage through which the electrophoresis sieving polymer must travel during loading.

Regardless of whether the sample processing devices include a valve or a constricted passage, rotation of the sample processing device with the electrophoresis sieving polymer located therein for delivery to the electrophoresis channels provides a significant advantage in that the fluid pressure generated in the electrophoresis sieving polymer during rotation before the electrophoresis sieving polymer passes through the flow restrictor (e.g., while the valve is closed) substantially, if not completely, removes any bubbles sufficiently large to adversely affect the separation to be performed in the electrophoresis channel.

Another advantage of sample processing devices according to the present invention is that even if bubbles or voids are located in the electrophoresis channels after loading with electrophoresis sieving polymer, the bubbles or voids may be removed by further rotation of the sample processing device. In other words, what could be considered a failure during loading can be corrected by additional rotation of the sample processing device (in contrast to the known methods and devices in which the electrophoresis channel must be emptied and reloaded or simply discarded).

In one aspect, the present invention includes a method of providing an electrophoresis channel containing an electrophoresis sieving polymer by providing a device having a plurality of electrophoresis channels and at least one electrophoresis medium chamber; providing electrophoresis sieving polymer in the at least one electrophoresis medium chamber; and rotating the device about an axis of rotation while the at least one electrophoresis medium chamber is in fluid communication with each electrophoresis channel of the plurality of electrophoresis channels, wherein the at least one electrophoresis medium chamber is located radially inward from the plurality of electrophoresis channels relative to the axis of rotation. During rotation of the device, the electrophoresis sieving polymer in the at least one electrophoresis medium chamber moves into the plurality of electrophoresis channels.

In another aspect, the present invention includes a method of providing an electrophoresis channel containing an electrophoresis sieving polymer by providing a

FIG. 2 is a plan view of the opposing side of the sample processing device of FIG. 1.

FIG. 3 is an enlarged view of a portion of one process array on the sample processing device of FIG. 1.

FIG. 3A depicts one exemplary flow restriction in the form of a constricted passage along a channel through which electrophoresis sieving polymer moves during loading of an electrophoresis channel.

FIG. 4 is an enlarged cross-sectional view of a valved process chamber in the process array of FIG. 3 (taken along line 4-4 in FIG. 3).

FIG. 5 is an enlarged cross-sectional view of an outermost process chamber in the process array of FIG. 3 (taken along line 5-5 in FIG. 3).

FIG. 6A is an enlarged cross-sectional view of an electrophoresis channel in the sample processing device of FIG. 1 (taken along line 6-6 in FIG. 1).

FIG. 6B is a cross-sectional view of an alternative electrophoresis channel construction.

FIG. 7 is a plan view of an alternative sample processing device according to the present invention.

FIG. 8 is a plan view of an alternative sample processing device according to the present invention.

FIG. 9 is a plan view of an alternative sample processing device according to the present invention.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides sample processing devices including integral electrophoresis channels and methods of using the same. The electrophoresis channels may be arranged on the sample processing device in any desired relationship such that rotation of the sample processing device can be used to load the electrophoresis channels with electrophoresis sieving polymers. Different illustrative designs of sample processing devices are depicted in the figures and described herein, although it should be understood that alternative arrangements of electrophoresis channels may be provided in sample processing devices according to the present invention.

device if rotated, a chamber in which the product of a process is collected, a chamber in which materials are filtered, etc.

The process arrays in sample processing devices of the present invention are arranged such that rotation of the sample processing devices facilitates the transfer of materials within the process arrays. It may be preferred that the process chambers 20 be arranged in a generally radial manner as seen in FIG. 1, such that as the sample processing device 10 is rotated about a central axis of rotation 11, sample materials in the process arrays are driven in the direction of the outermost process chamber 20d. In many instances, the innermost process chamber 20a may be referred to as a loading chamber, i.e., a chamber into which sample materials may be first introduced into the process array.

Although each of the process arrays of sample processing device 10 is depicted as being independent of the other process arrays (i.e., not in fluid communication with the other process arrays), it should be understood that one loading chamber may be used to supply process chambers in two or more process arrays. In such an instance, the process arrays may be fed by what can be referred to as a common loading chamber.

The process chambers 20 in each process array are sequentially connected by distribution channels 30a, 30b and 30c (commonly referred to below as distribution channels 30). The distribution channels 30 may be normally open between process chambers 20, for example, distribution channel 30a is normally open between process chambers 20a and 20b. As a result, rotation of the sample processing device 10 about axis of rotation 11 will typically cause materials in the innermost process chamber 20a to move towards process chamber 20b through distribution channel 30a.

It should be understood that although the process arrays of the depicted sample processing devices include distribution channels between the process chambers, within the array, it may be possible to provide process arrays on devices in accord with the present invention that are connected directly with each other, i.e., the process chambers may not be separated by a distribution channel or other fluid pathway. At least some separation between process chambers within the process arrays may, however, be preferred.

FIG. 4 is a cross-sectional view of the valved process chamber 20b in the process array of FIG. 3 and depicts a number of other features of one potential construction of a device that could be used in connection with the present invention. The construction of the sample processing device 10 includes a core 80 in which the features of the device are

which in a generally circular process chamber 20b extends around the entire periphery of the process chamber 20b (with the periphery of the process chambers 20b and 20c being depicted in a combination of solid and broken (hidden) lines in FIG. 3). It will be understood that other process chambers may have a sidewall that is broken into segments, e.g., a triangle, a square, etc.

The boundaries of the process chamber 20b are defined by the opening of the process chamber 20b onto the bottom surface 88 of the core 80. The lip 40 is in the form of an undercut extension into the volume of the process chamber 20b as seen in, e.g., FIG. 4. As a result, a portion of the volume of the process chamber 20b is located between the lip 40 and the cover 86.

A portion of the distribution channel 30b extends into the lip 40, with the opposite end of the distribution channel 30b being located in the next process chamber 20c. Where the distribution channel 30b extends onto the lip 40, an area 42 is formed with a reduced thickness relative to a remainder of the lip 40.

When an opening is provided in the lip 40 within the area 42 occupied by the distribution channel 30b, sample materials in the process chamber 20b can move into the distribution channel 30b for delivery to process chamber 20c. In the absence of an opening in the lip 40, movement of materials into process chamber 20c through distribution channel 30b is prevented by the lip 40 which otherwise seals against the cover 84 to prevent the flow of sample materials from process chamber 20b into the distribution channel 30b.

Openings in the lip 40 can be formed by any suitable technique or techniques. For example, the lip 40 may be mechanically pierced, ablated with laser energy, etc. In other embodiments, a valve structure may be incorporated in the lip 40 such that when the valve structure is opened, materials can move from the process chamber 20b into the distribution channel 30b. Examples of some valve structures may include foams, shape memory materials, etc. as described in, e.g., U.S. Patent Application Serial No. 09/894,810 filed on June 28, 2001 and entitled ENHANCED SAMPLE PROCESSING DEVICES, SYSTEMS AND METHODS.

The reduced thickness of the lip 40 in the area 42 occupied by the distribution channel 30b may provide a number of advantages. It may, for example, limit the location or locations in which the lip 40 may be easily pierced or otherwise deformed to provide

of the process chamber 20d is also in fluid communication with electrophoresis channel 50. Although the channels 30c, 50, and 72 are not in the same plane and would not typically be seen in a single cross-sectional view, they are all depicted in FIG. 5 for the sake of brevity in describing the construction of the sample processing device 10.

The sample processing devices of the present invention are constructed to allow for simplified loading of the electrophoresis sieving polymers into the electrophoresis channels 50. In addition, the construction of the sample processing devices and their integral electrophoresis channels allows for the loading of electrophoresis sieving polymers in a manner that results in substantially bubble-free electrophoresis sieving polymers in the electrophoresis channels 50. To accomplish simplified, substantially bubble-free loading of the electrophoresis sieving polymers in the electrophoresis channels, the present invention relies on centrifugal forces generated by spinning the sample processing devices.

In the illustrated embodiment, the electrophoresis channel loading structure includes an electrophoresis medium chamber 70 located radially inward from the electrophoresis channel 50 (relative to the axis of rotation 11). It may be preferred that some flow restriction be provided in the electrophoresis channel 50 or in the distribution channel 72 leading from the electrophoresis medium chamber 70 to the electrophoresis channel 50 to provide sufficient back pressure during loading of the electrophoresis sieving polymers from the electrophoresis medium chamber 70 into the electrophoresis channel 50. Gas bubbles trapped in the electrophoresis sieving polymer can be driven out of the system (back towards the chamber 70) during centrifugal loading of the electrophoresis sieving polymer into the electrophoresis channel 50 when sufficient back pressure is developed as the sample processing device 10 rotates.

In the depicted sample processing device 10, the flow restriction is provided by a valve 74 located between the electrophoresis medium chamber 70 and the electrophoresis channel 50. When the sample processing device 10 is rotated with electrophoresis sieving polymer in the electrophoresis medium chamber 70 while the valve is closed, the fluid pressure generated within the electrophoresis sieving polymer is preferably sufficient to force substantially all of the bubbles out of the electrophoresis sieving polymer. After the bubbles have been removed, the valve 74 can be opened and the electrophoresis sieving polymer loaded into the electrophoresis channel 50.

beneficial to rotate the device faster during the bubble removal stage if, e.g., a flow restriction such as a valve must be opened to allow the electrophoresis sieving polymer to enter the electrophoresis channel.

Further, the loading of electrophoresis sieving polymers into electrophoresis channels 50 may be facilitated by alternately accelerating and decelerating the sample processing device 10 during rotation, essentially burping the electrophoresis sieving polymers through the electrophoresis channels 50. The rotating may be performed using at least two acceleration/deceleration cycles, i.e., an initial acceleration, followed by deceleration, second round of acceleration, and second round of deceleration. It may further be helpful if the acceleration and/or deceleration are rapid. The rotation may also preferably only be in one direction, i.e., it may not be necessary to reverse the direction of rotation during the loading process.

The actual acceleration and deceleration rates may vary based on a variety of factors such as temperature, size of the sample processing device, distance of the electrophoresis channel from the axis of rotation, materials used to manufacture the sample processing devices, properties of the electrophoresis sieving polymers (e.g., viscosity), etc.

The rotational nature of the electrophoresis sieving polymer loading process in sample processing devices of the present invention provides an advantage in that if a void or bubbles are found in the electrophoresis channels after loading with electrophoresis sieving polymer, additional rotation of the sample processing device may be used to remove the void or bubbles. In some methods of the invention, the initial rotational loading procedure may be followed by an inspection for voids or bubbles in the electrophoresis sieving polymer within the electrophoresis channels. If a void or bubbles are detected during the inspection, the sample processing device may be rotated again in an attempt to remove the void or bubbles. The secondary rotation may or may not be accompanied by the delivery of additional electrophoresis sieving polymer to the electrophoresis channels.

It may be preferred that the electrophoresis channel 50 be curved in an arc that follows the curvature of the periphery of the sample processing device 10 as seen in, e.g., FIG. 1, but the electrophoresis channel 50 may take other shapes. If the electrophoresis channel 50 is to follow the curvature of a generally circular sample processing device 10,

take any suitable shape. For example, it may be desirable in some instances to provide an electrophoresis channel 50 with a more rounded bottom.

The alternative construction for an electrophoresis channel 150 seen in FIG. 6B includes a capillary or other tubing 152 located within a slot 154 formed in the core 180 of a sample processing device. The actual electrophoresis channel 150 is formed within the tubing 152, while the slot 154 is provided to hold the tubing in place.

One potential advantage of this construction is that the materials for the tubing 152 can be selected for compatibility with the electrophoresis process while the materials for the core 180 can be selected for other properties as desired. Further, it may be easier to accurately control the size of the inner diameter of the tubing 152 than to control the size of the slot 154 formed in the core 180. Another potential advantage of the construction depicted in FIG. 6B is that the size of the electrophoresis channel 150 can be varied by providing tubing 152 with a different wall thickness. As a result, a single core 180 with a slot 154 of one size may be used with tubing that has different inner diameters but the same outer diameter to provide electrophoresis channels 150 with different cross-sectional dimensions.

Another optional feature depicted in FIG. 6B is a cover film 184 located over the slot 154. The cover film 184 may be useful in retaining the tubing 152 within the slot 154 and/or protecting it from damage during use. The cover film 184 may be attached to the core 180 by any suitable technique, e.g., adhesives, welding (thermal, chemical, etc.), etc. Another option to the cover film 184 is that the tubing 152 may be retained within the slot 154 by, e.g., an adhesive such as, e.g., an optical grade epoxy.

The substrates, cover films, tubing and other components used in connection with the sample processing devices of the present invention may be manufactured of a variety of different materials, provided that the materials used are compatible with the various sample materials, reagents, etc. that may come in contact with the various materials. In addition to compatibility issues, the materials used in connection with the sample processing devices of the invention may be selected for other properties, such as transparency to electromagnetic energy of selected wavelengths, absorption of electromagnetic energy of selected wavelengths, reflectivity of electromagnetic energy of selected wavelengths, heat transfer properties, thermal mass properties, etc. For example,

reaction mixtures, e.g., nucleic acid amplification, which may or may not also be carried out in process chambers of the device. Some or all of the required reagents may be present in the device as manufactured, they may be loaded into the process chambers after manufacture of the device, they may be loaded in the process chambers just before introduction of the sample, or they may be mixed with sample before loading into the process chambers.

One method using a sample processing device according to the present invention may include starting with sample material, e.g., lysed blood cells, that are provided in a loading chamber on the device. Referring to, e.g. FIG. 1, the innermost process chamber 20a may serve as a convenient loading chamber in such a method. A filter (not shown) may preferably be provided to filter the starting sample material as it moves from the loading chamber 20a to the next process chamber 20b through distribution channel 30a. Movement or transfer of the sample materials from the loading chamber 20a to the process chamber 20b may preferably be accomplished by rotating the sample processing device 10 about the axis of rotation 11.

The process chamber 20b may preferably include suitable polymerase chain reaction (PCR) primers as supplied, e.g., dried down in each of the chambers 20b. Each of the chambers 20b may include the same primer or different primers depending on the nature of the investigation being performed on the starting sample material. One alternative to providing the primers in the process chambers before loading the sample is to add a suitable primer to the loading chamber 20a with the starting sample material (provided that the primer is capable of passing through the filter, if present).

After locating the starting sample material and any required primers in the process chambers 20b, the biological mixtures in the process chambers 20b are thermally cycled under conditions suitable for PCR amplification of the selected genetic material. Such thermal cycling may preferably occur while the sample processing device 10 is rotated as described in some of the references identified above.

Rotation of any sample processing device 10 during the PCR process (or at any other desired time) may be used to facilitate mixing through mechanical agitation of the sample materials and any other materials (e.g., reagents, etc.) present in the process chambers. The mechanical agitation may be accomplished by oscillating the sample processing device 10 in opposite directions about the axis of rotation 11. The oscillations

sequence cycling reaction products through, e.g., another filter chamber (not shown) to remove unwanted materials from the sequencing ladders (e.g., sequencing primers, ddNTPs, etc.). The filter chambers may, e.g., contain active chemistry coated on surfaces of the chamber, for example. Alternatively, or additionally, they may contain solid-phase materials for sample clean-up (e.g., dye removal).

After moving the sample materials into the outermost process chamber 20d, the target DNA materials in the sample can be moved into the electrophoresis channel 50 by any number of techniques. Typically, however, the electrophoresis channel 50 will be separated from the process chamber 20d by, e.g., a porous plug 44or other barrier that can prevent flow of the electrophoresis sieving polymers into the process chamber 20d during loading of the electrophoresis channel 50 and also prevent the passage of unwanted materials from the process chamber 20d into the electrophoresis channel 50.

One technique that can be used to move the target DNA materials through the porous plug and into the electrophoresis channel 50 is electrokinetic injection. For example an electrode located within the process chamber 20d could be used in connection with a second electrode located within the electrophoresis channel 50. By applying the appropriate voltages to the electrodes, the target DNA material within the process chamber 20d can be moved through the porous plug and into the electrophoresis channel 50 where separation can occur. Other potentially suitable techniques that could be used in place of electrokinetic injection through a porous plug include, but are not limited to, hydraulic loading, valving, etc.

The actual techniques of performing sequencing separations in the electrophoresis channel 50 are substantially similar to the techniques used when performing sequencing separations using conventional equipment, devices and techniques. For example, a first electrode 56 may be provided in electrical communication with the electrophoresis sieving polymer in the electrophoresis channel 50 proximate the process chamber 20d. The first electrode 56 may be attached to the sample processing device 10 such that it forms an integral part of the device 10, or it may be provided separately as, e.g., a probe inserted into the electrophoresis channel 50 proximate the process chamber 20d. The exact construction and/or form of the electrode will be known to those skilled in the art of electrophoresis separation methods.

Another illustrative variation in the sample processing devices of the present invention is depicted in FIG. 8, in which a sample processing device 310 includes a number of electrophoresis channels 350 arranged such that they include an inner process chamber 320a located proximate the axis of rotation 311 and an outer process chamber 320b located further away from the axis of rotation 311 than the inner process chamber 320a. As a result, materials located within inner process chamber 320a can be loaded in the electrophoresis channels 350 by rotation of the sample processing device 310 about the axis of rotation 311. Although the electrophoresis channels 350 are not located along geometrically accurate radial lines, the electrophoresis channels 350 will be considered to be arranged "generally radially" for the purposes of the present invention. It will be understood that in the simpler construction depicted in FIG. 8, the inner process chamber 320a can function as both the entry point for the electrophoresis sieving polymer (i.e., the process chamber functions as the electrophoresis medium chamber), as well as the entry point for the sample materials to be processed using the electrophoresis channels 350.

FIG. 9 depicts another alternative sample processing device 410 according to the present invention. The sample processing device 410 includes a plurality of electrophoresis channels 450 extending generally radially outward from the axis of rotation 411 of the sample processing device 410. Each of the electrophoresis channels 450 emanates from a central process chamber 420a provided in the shape of a ring and terminates in a process chamber 420b.

All of the electrophoresis channels 450 are in fluid communication with the single process chamber 420a, although it should be understood that in sample processing devices of the present invention two or more process chambers could be provided in place of the single process chamber 420a, with each of the two or more process chambers being in fluid communication with two or more of the electrophoresis channels 450.

As with FIG. 8, it will be understood that in the simpler construction of FIG. 9, the inner process chamber 420a can function as both the entry point for the electrophoresis sieving polymer (i.e., the process chamber functions as the electrophoresis medium chamber), as well as the entry point for the sample materials to be processed using the electrophoresis channels 450.

As discussed above, the electrophoresis channels depicted in connection with FIGS. 1 and 2 are preferably vented proximate their terminal ends (i.e., the ends distal

CLAIMS:

1. A method of providing an electrophoresis channel containing an electrophoresis sieving polymer, the method comprising:

providing a device comprising a plurality of electrophoresis channels and at least one electrophoresis medium chamber;

providing electrophoresis sieving polymer in the at least one electrophoresis medium chamber; and

rotating the device about an axis of rotation while the at least one electrophoresis medium chamber is in fluid communication with each electrophoresis channel of the plurality of electrophoresis channels, wherein the at least one electrophoresis medium chamber is located radially inward from the plurality of electrophoresis channels relative to the axis of rotation;

wherein the electrophoresis sieving polymer in the at least one electrophoresis medium chamber moves into the plurality of electrophoresis channels during the rotating.

2. A method according to claim 1, wherein the plurality of electrophoresis channels are arranged generally radially with respect to the axis of rotation.

3. A method according to claim 1, wherein at least a portion of the rotating is performed while preventing movement of the electrophoresis sieving polymer into at least one electrophoresis channel of the plurality of electrophoresis channels.

4. A method according to claim 3, wherein the preventing comprises holding a valve in a closed configuration between the at least one electrophoresis medium chamber and the at least one electrophoresis channel.

5. A method according to claim 4, further comprising opening the valve between the at least one electrophoresis medium chamber and the at least one electrophoresis channel, wherein the electrophoresis sieving polymer moves into the at least one electrophoresis channel.

6. A method according to claim 1, further comprising:

11. A method according to claim 9, further comprising rotating the sample processing device while preventing movement of the electrophoresis sieving polymer into at least one electrophoresis channel of the plurality of electrophoresis channels.

12. A method according to claim 11, wherein the preventing comprises holding a valve in a closed configuration between the at least one electrophoresis medium chamber and the at least one electrophoresis channel.

13. A method according to claim 12, further comprising opening the valve between the at least one electrophoresis medium chamber and the at least one electrophoresis channel, wherein the electrophoresis sieving polymer moves into the at least one electrophoresis channel.

14. A method according to claim 9, further comprising:

inspecting the plurality of electrophoresis channels for gas bubbles in the electrophoresis sieving polymer within the plurality of electrophoresis channels after rotating the device; and

rotating the device about the axis of rotation after inspecting if the inspecting reveals gas bubbles.

15. A method according to claim 9, wherein the rotating comprises at least two acceleration/deceleration cycles.

16. A method according to claim 9, wherein the electrophoresis sieving polymer moves in a generally radial direction relative to the axis of rotation when the electrophoresis sieving polymer in the at least one electrophoresis medium chamber moves into the plurality of electrophoresis channels during the rotating.

17. A device for processing sample material, the device comprising:

a substrate comprising first and second major surfaces and a hub defining an axis of rotation for the substrate;

23. A device according to claim 17, wherein the plurality of electrophoresis channels comprise a plurality of capillary tubes attached to the substrate.

24. A device according to claim 17, wherein the connection structure comprises a porous plug.

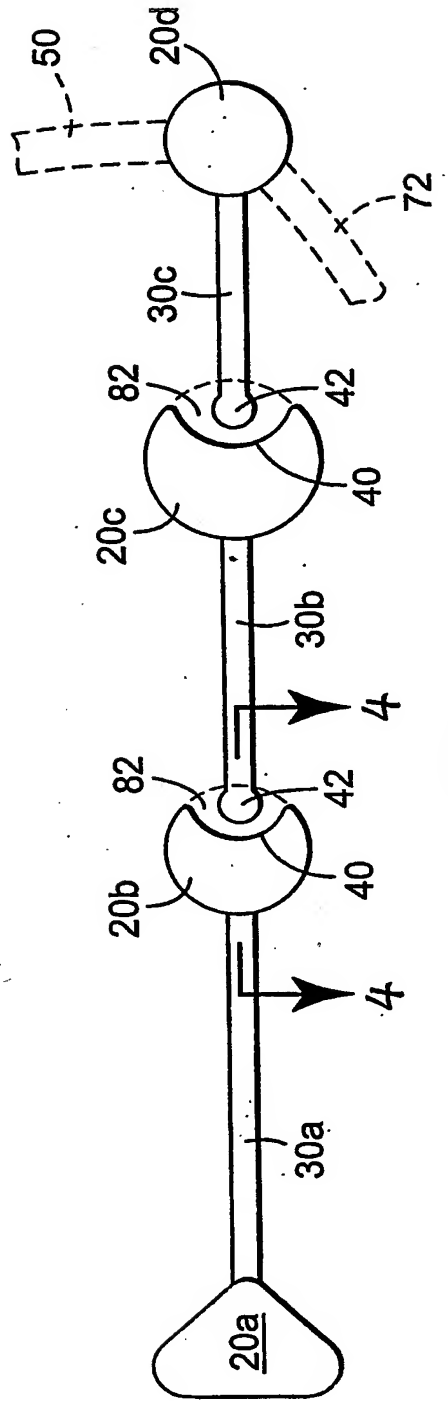

FIG. 3

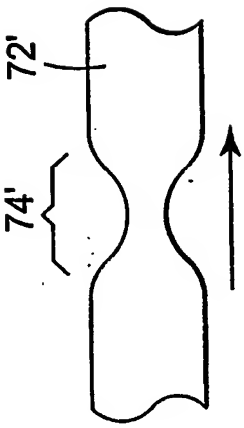

FIG. 3A

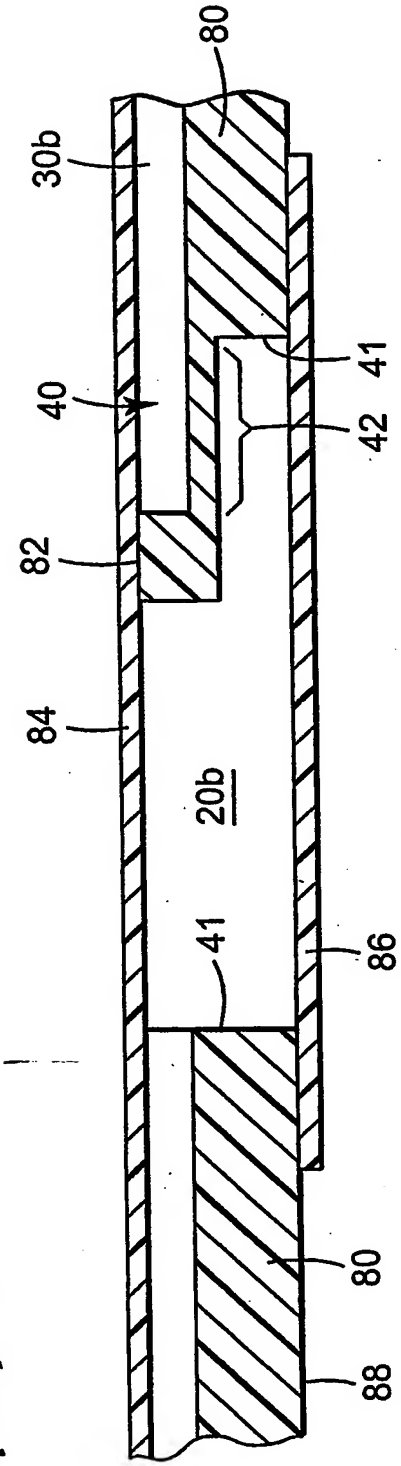

FIG. 4

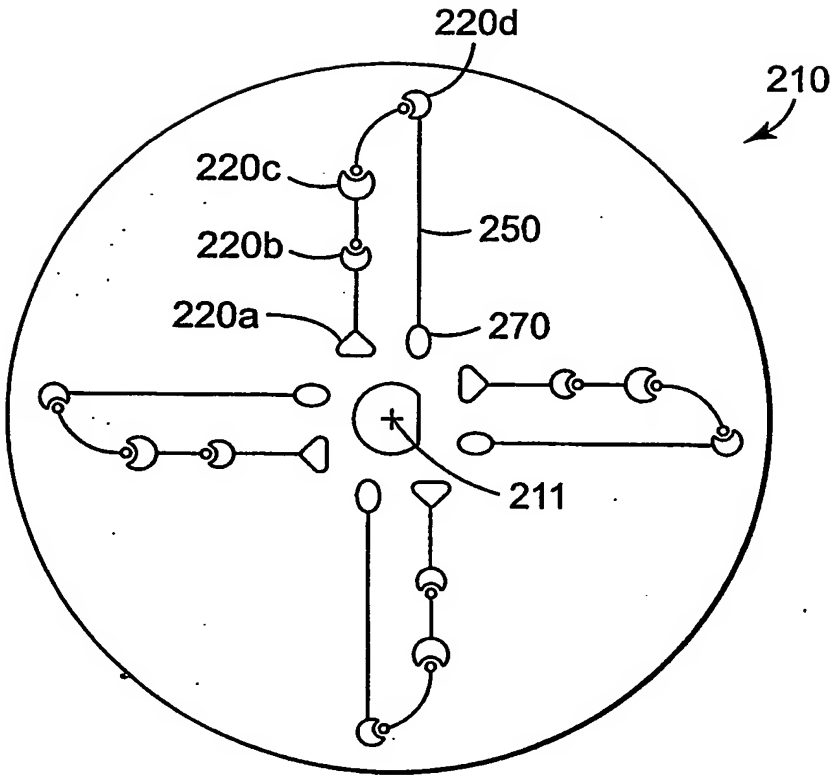

FIG. 7

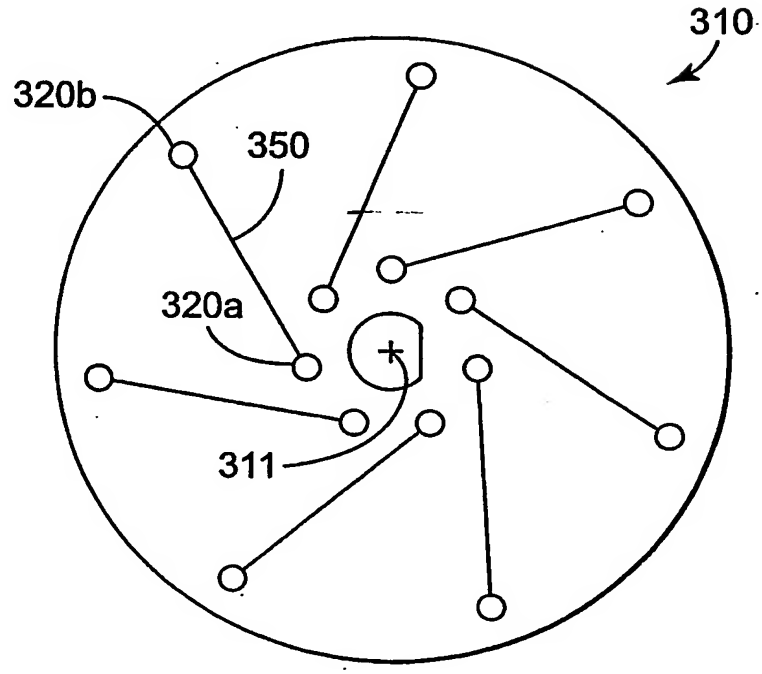

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/37970

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :G01N 27/00
US CL :141/34, 1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 141/34, 1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,017,765 A (YAMADA et al.) 25 January 2000.	1-16
A	US 4,708,782 A (ANDRESEN et al.) 24 November 1987.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
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